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Original Article

Early metabolic response after laparoscopic sleeve gastrectomy in obese diabetes.

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Abstract

Objective**:** Authors investigated whether laparoscopic sleeve gastrectomy (LSG), one of the bariatric surgeries, in obese type 2 diabetes patients would show a metabolic improving effect at an early stage after surgery.
Method**:** LSG was conducted for five morbidly obese subjects whose BMI was more than 35 and were diagnosed with type 2 diabetes. The glycemic markers, lipids and hepatic functions were checked before, one, two and three months after surgery.
Results**:** Hemoglobin Alc level remarkably decreased from 8.7% to 5.9% ($p < 0.001$) one month after surgery, compared with before surgery, and the effect was kept at a level of lower than 6.0%, such as 5.8% and 5.6%, two months and three months after surgery. The average of fasting plasma glucose level significantly decreased to 87 mg/dL, 94 mg/dL and 89 mg/dL from 184 mg/dL ($p < 0.001$), and it was kept under 100 mg/dL. BMI continued to decrease from 39.9 kg/m^2 to 32.3 kg/m^2, 30.0 kg/m^2 and 28.8 kg/m^2 on average, every month. The decrease rates of BMI and HbAlc after surgery did not correlated with each other. No improvement effect was recognized in total cholesterol level after surgery. Triglyceride significantly decreased from one month after surgery ($p < 0.001$). Aspartate transaminase and alanine transaminase levels significantly decreased from two months after surgery ($p < 0.05$, $p < 0.01$).
Conclusion**:** As a result, it was suggested that disregarding weight decrease, LSG has a remarkable antidiabetic effect from an early stage of one month after surgery. During the observation period, LSG showed that it has the effect of improving triglyceride and hepatic function, and its effect on cholesterol is small.

KEY WORDS**:** obesity, type 2 diabetes, metabolic surgery, laparoscopic sleeve gastrectomy and bariatric surgery

Introduction

It was clarified that bariatric surgery has not only the effect of weight loss but also improvement of metabolism, and the number of surgery cases is increasing worldwide [1)]. However, it has not been generalized in Japan yet, and there have been only a few reports [2)]. Since April 2014, laparoscopic sleeve gastrectomy (LSG) has become applicable to health insurance in Japan. However, the facility standard for its purpose is very strict so that it cannot rapidly spread. Bypass surgeries, including Roux-en-Y gastric bypass (RGYB), have been recognized as effective in metabolic improvement [3-5)]. LSG started in full swing this century, and the number of surgery cases is increasing [6-7)]; however, many questions remain unsolved. Diabetes is a common disease with strong glycative stress. As the Japanese have a national trait which makes it likely for them to develop diabetes for their degree of obesity, Western data may be unable to be directly applied to them. Because LSG's effects that occur in an early stage in obese Japanese people with diabetes, in particular, were not clarified in many respects, the authors conducted the research on the antidiabetic effects of LSG for obese and type 2 patients in an early stage after surgery.

Methods

Five cases of morbidly obese patients diagnosed with diabetes, out of 13 cases of LSG conducted by the same surgeon from August 2014 to July 2016 in Takeda General Hospital, were subjected to this research. The profiles of each case are shown in ***Table 1***. The number of male subjects was one and that of the females was four; their average age was 39.6 ± 0.8 years, the averages of body weight and body mass index (BMI) were 107.4 ± 7.0 kg and 39.9 ± 0.8 kg/m^2, respectively. Each case was treated by medical therapy,

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Table 1. Characteristics of the patients at baseline.

Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5
Age (year)	41	39	41	40	37
Gender	Male	Female	Female	Female	Female
BMI	40	42	41	37	40
Body weight (kg)	130	108	107	97	95
Duration of diabetes (year)	3	10	5	11	6
Use of insulin	—	—	—	33 units	—
Diabetes medications	GLP-1 receptor agonist	SU TZD	Biguanide SGLT-2 inhibitor	SU DPP-4 inhibitor	Biguanide DPP-4 inhibitor
Waist circumstance (cm)	112	113	117	118	111
Smoker	former	never	former	never	never
History of dyslipidemia	+	+	+	+	+
History of hypertension	—	—	+	+	+

The body mass index (BMI) is the weight in kilograms (kg) divided by the square of the height in meters (m).
GLP-1, glucagon-like peptide-1; SU, sulfonylurea; TZD, thiazolidine; SGLT-2, sodium-dependent glucose transporter 2; DPP-4, dipeptidyl peptidase-4.

such as multidrug therapy or multiple insulin therapy, based on dietary therapy and exercise therapy. However, due to treatment resistance and repeatedly rebounded weight loss treatment, surgical therapies were applied. Case 2 and Case 4 had long diabetic histories of more than 10 years. Case 2 started to be treated with α-glucosidase inhibitor; however, because blood glucose control was not good, the treatment was replaced with a therapy combining sulfonylurea and thiazolidine. However, due to the developments of edema and liver damage, it was changed to a therapy only with sulfonlurea. Case 4 was treated with Noborabit, 15 units, and Nobrinn, 18 units, in addition to multidrug therapy; however the patient's HbAlc level was very high at 11.3, and the patient suffered peripheral nerve disorder, retinopathy of diabetes and diabetic nephropathy. The conditions that can be adapted to bariatric surgery in Japan is that despite undergoing medical therapy for more than six months, enough weight loss cannot be obtained, BMI is more than 35 and one or more complications associated with diabetes, hypertension and hyperlipidemia develop. All patients met these conditions.

Every month for three months after and before surgery, Hemoglobin Alc (HbA1c) [NGSP] and fasting plasma glucose (FPG) as BMI and glucose metabolic maker; total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL) and triglyceride (TG) as lipid indicators; and aspartate transaminase (AST), alanine transaminase (ALT) and gamma glutamyl transpeptidase (γ-GPT) as evaluation of liver function.

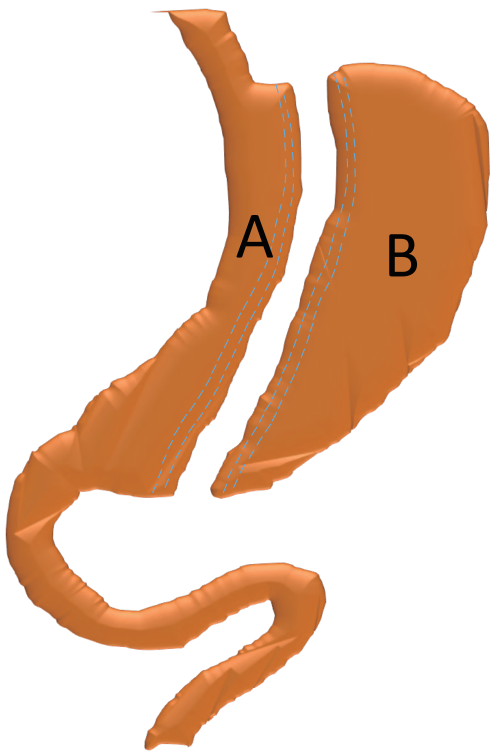

Fig. 1. **Laparoscopic sleeve gastrectomy.**

A: new stomach pouch. B: stomach removed

Surgical technique

LGS is a surgery method to remove the side of the greater curvature of the stomach and create a banana-shaped stomach (***Fig. 1***). All surgeries are conducted by the laparoscopic five-port approach in the position with the head up (in Fowler's position) in order to reduce the burden on the lungs. Separate the greater omentum along the stomach wall in the cranial direction, using an ultrasonic coagulation incision device. Separate the greater omentum up to the His angle at a proximal part of the stomach and up to about 4 cm from the oral side from the pyloric ring at a distal part. Ask a gastroenterologist to insert an endoscope up to the pyloric region, and fixate it at the side of the lesser curvature. The endoscope can be followed as a guide to cutting off the stomach using an autosuture. Reinforce the staple line by continuous suture using 3-0 absorbing thread. Confirm the presence or absence of constriction and bleeding and that the stapler does not become lodged in the esophagus. Retain the drain along the cutting line of the stomach.

Ethical consideration

Written informed consent was obtained from each subject before the start of this study, which was approved by the Ethics Committee of our hospital and also was in accordance with the Helsinki Declaration of 1975, as revised in 1983.

Statistical analysis

All results are expressed as means ± standard error of the mean. Statistical analysis was made with analysis of variance, and Pearson correlation coefficients were calculated. Statistical significance was obtained when the p value was < 0.05.

Results

LSG could be performed completely endoscopically in all five cases. The average surgical time was 210 ± 20 minutes. The amount of bleeding was too small to measure. Fluid diet started on the second day after surgery. The average hospital stay was 10 ± 1 days. The progress after surgery was good and no complications were recognized. All oral medicines, including diabetes drugs and injection drugs, including insulin, could be stopped in all cases.

In ***Figures 2, 3*** and ***4***, the changes in BMI, HbAlc and FPG one, two and three months after surgery are shown. BMI significantly changed from 39.5 ± 0.9 kg/m^2 before surgery to 32.3 ± 1.4 kg/m^2 one month after surgery ($p < 0.001$), and continued to decrease to 30.0 ± 0.9 kg/m^2 two months after surgery and to 28.8 ± 0.9 kg/m^2 three months after surgery. It furthermore significantly decreased three months after surgery compared to one month after surgery ($p < 0.05$).

HbAlc significantly decreased one month after surgery from 8.7 ± 0.9% before surgery ($p < 0.001$), and remarkably improved to 5.9 ± 0.3%. It was 5.8 ± 0.3% two months after surgery and 5.6 ± 0.4% three months after surgery, which showed that an improvement effect of less than 6% was maintained. FPG significantly decreased from 184 ± 19.8 mg/dL before surgery ($p < 0.001$), and remarkably improved to 87 ± 7.6 mg/dL. It was 94 ± 1.9 mg/dL two months after surgery and 89 ± 5.5 mg/dL three months after surgery, which showed that it was kept at less than 100 mg/dL after surgery.

As shown in ***Table 2***, there was no correlation between the decreased rate of BMI and that of HbAlc. A correlation between the decreased rate of BMI and that of FPG was observed one month after surgery, but not observed between others.

As shown in ***Table 3***, there was no correlation between the decreased rate of HbAlc and that of FPG.

Table 4 shows the changes in lipids and hepatic function before and after LSG surgery. Regarding lipids, there were no large changes in TC and LDL, rather, they worsened. Improvement effects were recognized in HDL two to three months after surgery from one month after surgery ($p < 0.05$, $p < 0.01$). TG significantly decreased starting one month after surgery ($p < 0.001$) and it was kept at low levels until three months after surgery. Regarding hepatic function, both AST and ALT decreased from the second month after surgery and improvement effects were recognized. γ-GTP showed a trend toward improvement; however, no significant difference was observed.

Discussion

It was clarified in this research that LSG has remarkable improvement effects on obese and diabetic patients during the early stage one month after surgery. In addition, it makes it possible to stop the use of diabetic drugs; its benefit is great from the viewpoints of medical economics [8]. According to the American Diabetes Association (ADA), the definition of complete remission of diabetes is that HbAlc is less than 5.7% and FPG is less than 100 mg/dL. That of improvement of diabetes is that HbAlc is 5.7% - 6.5% and this condition can be maintained at least a year without treatment drugs [9]. According to this definition, the cases in this research achieved improvement and remission one month after surgery, and the processes after surgery of these cases are to be observed one year from now. HbAlc reflects the blood glucose level one to two months before, which shows improvement effects that cannot be explained by dietary limitations only. Because the Japanese show metabolic improvement effects with several kilograms of weight loss, HbAlc may have improved earlier compared to the speed of weight loss.

In the case of bariatric bypass surgeries including BYGB, regarding diabetes improvement effects after surgery, the changes of incretin were paid attention to and the foregut theory [10] and hindgut theory [11] are proposed [12]. However, through what mechanism does LSG show its antidiabetic effects? The characteristics of sleeve surgery are comparatively simple and clear, and compared with bariatric bypass surgery, it has only a few complications after surgery. Its weight loss effect can be expected enough that it is said to be better suited for cases that are more likely to be complicated with the disorders associated with obesity despite a low degree of obesity, like that of the Japanese.

Generally it is understood that creating a banana-shaped stomach is aimed at restricting the intake of food and losing some weight, but it is said that an appetite stimulating hormone called ghrelin secrets in a large amount at the stomach fundus, so appetite can be reduced if it is removed. Ghrelin is also the hormone restricting the secretion of insulin, which suggests ghrelin's involvement in the mechanism of the amelioration of diabetes [13]. Recently, attention was paid to the fact blood bile acid increases after LSG surgery and in research conducted by Seeley *et al*., it was found that, in the experiment, using SG mice, the activities of farnesoid X receptor (FXR) were enhanced and large changes in metabolism, such as glucose tolerance, occurred. A mechanism that brings about changes

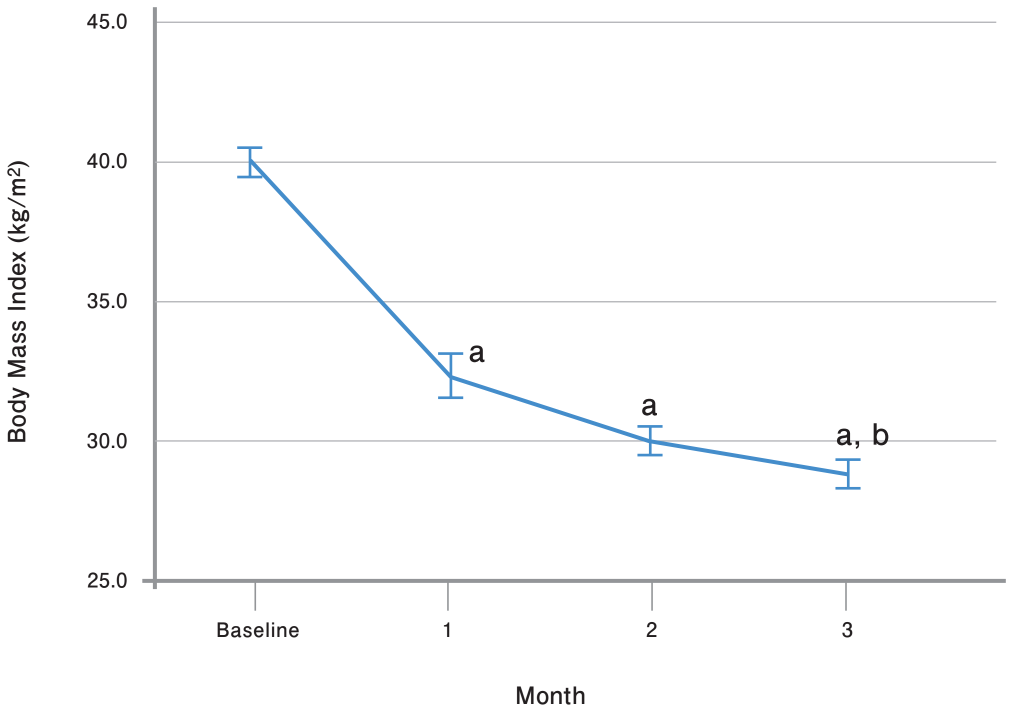

Fig. 2. **Changes in body mass index.**

Values are given as mean and SEM; a, significantly different from the preoperative value, $p < 0.001$; b, significantly different from value of first postoperative month. $p < 0.05$. SEM, standard error mean.

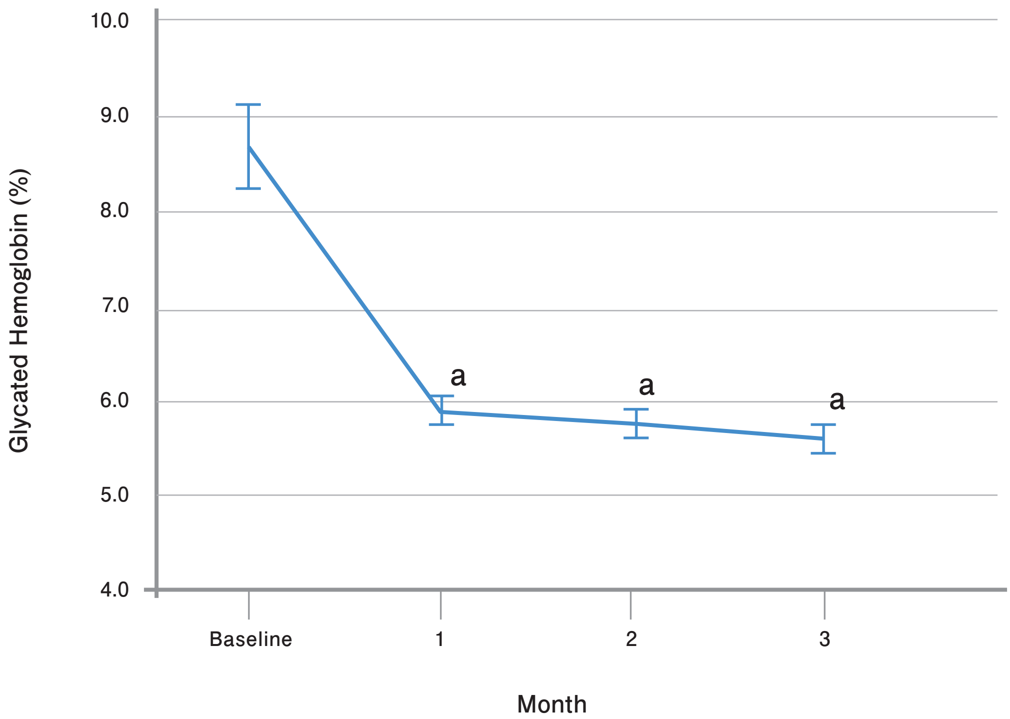

Fig. 3. **Changes in glycated hemoglobin.**

Values are given as mean and SEM; a, significantly different from the preoperative value, $p < 0.001$. SEM, standard error mean.

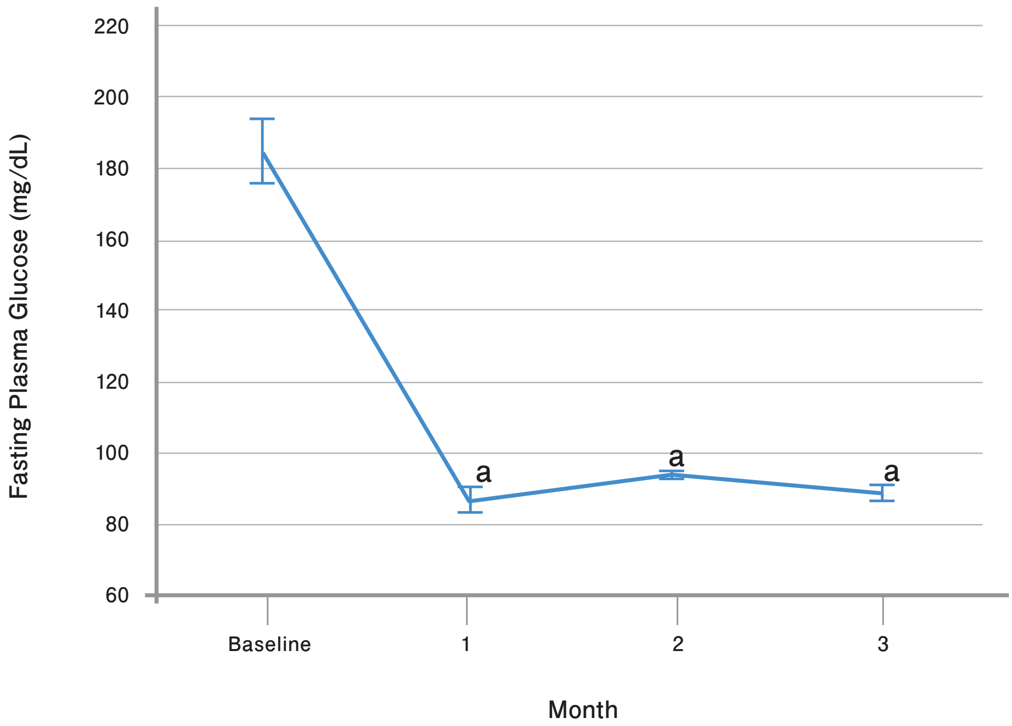

Fig. 4. **Changes in fasting plasma glucose.**
Values are given as mean and SEM; a, significantly different from the preoperative value, $p < 0.001$. SEM, standard error mean.

Table 2. Correlation of glycemic maker reduction with BMI reduction

	% BMI reduction --- 1 month		% BMI reduction --- 2 month		% BMI reduction --- 3 month	
	R^2	p value	R^2	p value	R^2	p value
% Hemogloblin A1c reduction	0.015	0.843	0.004	0.922	0.011	0.867
% FPG reduction	0.861	0.023	0.018	0.837	0.003	0.931

BMI, body mass index; FPG, fasting plasma glucose.

Table 3. Correlation of HbA1c reduction with fasting glucose reduction

	% HbA1c reduction --- 1 month		% HbA1c reduction --- 2 month		% HbA1c reduction --- 3 month	
	R^2	p value	R^2	p value	R^2	p value
% FPG reduction	0.713	0.072	0.745	0.060	0.162	0.502

HbA1c, glycated Hemoglobin; FPG, fasting plasma glucose.

Table 4. Changes in lipids and hepatic function following laparoscopic sleeve gastrectomy

Parameter	Unit	Baseline	1 month post operation	2 month post operation	3 month post operation
Lipids					
TC	mg/dL	211.6 ± 14.1	184.0 ± 6.5	225.8 ± 23.6	222.6 ± 21.9
HDL	mg/dL	52.2 ± 6.9	40.4 ± 4.6	59.4 ± 8.8 [a]	63.0 ± 7.6 [b]
LDL	mg/dL	130.2 ± 20.3	129.6 ± 3.2	160.5 ± 21.4	147.6 ± 20.2
TG	mg/dL	196.0 ± 15.2	94.4 ± 9.0 [c]	87.8 ± 8.8 [c]	89.8 ± 19.1 [c]
Hepatic function					
AST	U/L	36.2 ± 5.1	29.6 ± 4,2	22.0 ± 1.1 [d]	18.4 ± 2.6 [d]
ALT	U/L	52.4 ± 6.9	40.4 ± 10.8	23.0 ± 2.4 [e, f]	17.2 ± 2.2 [e, f]
γ-GTP	U/L	35.6 ± 11.0	24.4 ± 6.0	16.0 ± 1.7	14.8 ± 0.5

Values are given as mean ± SEM; a, significantly different from value of first postoperative month, $p < 0.05$; b, significantly different from value of first postoperative month, $p < 0.01$; c, significantly different from the preoperative value, $p < 0.001$; d, significantly different from the preoperative value, $p < 0.05$; e, significantly different from the preoperative value, $p < 0.01$; f, significantly different from value of first postoperative month, $p < 0.05$; g, significantly different from the preoperative value, $p < 0.001$.
SEM, standard error mean; TC, total cholesterol; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TG, triglyceride; AST, aspartate transaminase; ALT, alanine transaminase; γ-GTP, gamma-glutamyl transpeptidase.

in bacteria in intestines was presented [14]. In this research, the experiment used genetically modified FXR knockout mice and showed that the increase of bile acid was more essential than diet restriction effects because FXR knockout mice following SG did not show weight loss effects. It is reported that similarly to the case of bypass surgeries, the increase of incretins, such as glucagon-like peptide (GLP-1), were observed even after LSG [15].

Bile acid is shown to accelerate the secretion of GLP-1 through G-protein coupled receptor TGR5 so that the increased secretion of bile acid increases the secretion of GLP-1 and may be involved in the improvement of glucose tolerance [16, 17]. It has been discovered that bile acid works as an important adjusting factor for lipid, glucose and overall energy metabolisms. However, there are many unclear points regarding the mechanisms of antidiabetic effects of LSG at this time. It seems that various factors including gastrointestinal hormone, bacteria in intestines, bile acid, fat cells, fat metabolism, the nerve system, the endocrine system and inflammation are involved in it. It has been clarified that bypass surgeries and LSG are effective in the amelioration and remission of diabetes. The clarification of the mechanisms of antidiabetic effects by bariatric surgery will possibly lead not only to a measure to decide the adaptation of surgical treatment, but also the clarification of the clinical state of diabetes and the development of new drug therapies.

At an early stage after LSG, antidiabetic effects are shown and the responses of the lipid system should be paid special attention to. Roughly speaking, the lipid system consists of TC, HDL, LDL and TG. There was no significant change in TC level, HDL level was improved two to three months after surgery, LDL level tended to increase and TG level improved remarkably. This result is similar to that of the long-term research more than one year after LSG, which has been reported [18, 19]. The authors considered that as the intake of carbohydrates and animal fat decreased after LSG, due to diet restriction, the material for TG decreased and as a result the accumulation of TG in liver decreased, hepatic steatosis was improved and AST level and ALT levels became normal. LSG seemed to have weak response to cholesterol metabolism. Due to the increase of bile acid after LSG, the increase in the amount of enterohepatic circulation and the increase of cholesterol absorption may possibly be involved in cholesterol metabolism [20]. It is necessary to wait for the accumulation of long-term experiences in a number of cases, which will possibly become an important source of information to decide the adaptation of surgical treatment.

There are problems in this research, such as the information of patients' compliance and how eagerly they dealt with diet and exercise before and after surgery were not reflected in this research. The number of cases was also small. It is important to increase the number of cases in the future.

Conclusion

LSG showed remarkable antidiabetic effects one month after surgery without a direct relationship to weight loss. TC levels were improved one month after surgery and hepatic function was improved two months after surgery; however, there were no significant changes in TC and LDL during the observation period. From the fact that LGS showed remarkable antidiabetic effects one month after surgery without a direct relationship to weight loss, it was suggested that LSG may possibly be effective on the improvement of glycative stress.

Conflict of interest

The authors have no conflict of interest in this study.

References

1) Angrisani L, Santonicola A, Iovibo F, et al. Bariatric surgery worldwide 2013. Obes Surg. 2015; 25: 1822-1832.
2) Sasaki A, Wakabayashi G, Yonei Y. Current status of bariatric surgery in Japan and effectiveness in obesity and diabetes. J Gastroenterol. 2014; 49: 57-63.
3) Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: A systemic review and meta-analysis. JAMA. 2004; 292: 1724-1737.
4) Mingrone G, Panunzi S, De Gaelano A, et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. N Engl J Med. 2012; 366: 1577-1585.
5) Schauer PR, Kashyap SR, Wolski K et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. N Engl J Med. 2012; 366: 1567-1576.
6) Ren CJ, Patterson E, Gagner M. Early results of laparoscopic biliopancreatic diversion with duodenal switch: A case series of 40 consecutive patients. Obes Surg. 2000; 10: 514-523.
7) Dietel M, Crosby RD, Gagner M. The first consensus summit for sleeve gastrectomy (SG). New York City, October 25-27, 2007. Obes Surg. 2008; 18: 487-496.
8) Sussenbach SP, Padoin AV, Silva EN, et al. Economic benefits of bariatric surgery. Obes Surg. 2012; 22: 266-270.
9) American Diabetes Association. Standards-2012 of medical care in diabetes-2012. Diabetes Care. 2012; 35(Suppl 1): S11-S63.
10) Mason EE. The mechanisms of surgical treatment of type 2 diabetes. Obes Surg. 2005; 15: 459-461.
11) Rubino F, Gagner M. Potential of surgery for curing type 2 diabetes mellitus. Ann Surg. 2002; 236: 554-559.
12) Knop FK. Resolution of type 2 diabetes following gastric bypass surgery: Involvement of gut-derived glucagon and glucagonotropic signaling? Diabetologia. 2009; 52: 2270-2276.
13) Cummings DE, Weigle DS, Frayo RS, et al. Plasma ghrelin levels alter diet-induced weight loss or gastric bypass surgery. N Engl J Med. 2002; 346: 1623-1630.
14) Ryan KK, Tremaroli V, Clemmensen C, et al. FXR is a molecular target for the effects of vertical sleeve gastrectomy. Nature. 2014; 509: 183-188.
15) Ugi S, Yamamoto H, Kusunoki C, et al. Laparoscopic sleeve gastrectomy leads to rapid improvement of glucose tolerance and insulin secretion with enhanced glucagon-like peptide (GLP-1) secretion. Diabetol Int. 2010; 1: 99-103.
16) Katsuma S, Hirasawa A, Tsujimoto G. Bile acids promote glucagon-like peptide-1 secretion through TGR5 in a murine enteroendocrine cell line STC-1. Biochem Biophys Res Commun. 2005; 329: 386-390.
17) Knop FK. Bile-induced secretion of glucagon-like peptide-1: Pathophysiological implications in type 2 diabetes? Am J Physiol-Endocrinol Metab. 2010; 299: E10-E13.
18) Zhang F, Strain GW, Lei W, et al. Changes in lipid profiles in morbidly obese patients after laparoscopic sleeve gastrectomy (LSG). Obes Surg. 2011; 21: 305-309.
19) Golomb I, David MB, Glass A, et al. Long-term metabolic effects of laparoscopic sleeve gastrectomy. JAMA Surg. 2015; 150: 1051-1057.
20) Hofmann AF, Hargey LY. Bile acids: Chemistry, pathochemistry, biology, pathobiology, and therapeutics. Cell Mol Life Sci. 2008; 65: 2461-2483.